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Thrombin-induced Angiogenesis: Therapeutic Implications

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Clinical, laboratory, histopathological and pharmacological evidence support the notion that a systemic activation of angiogenesis is often present in cancer patients (1). In addition thrombin was shown to promote tumor progression and metastasis in animals and epidemiological studies suggest an increased risk of cancer diagnosis after primary thromboembolism (2).

We have proposed that the aforementioned results may be related to our finding that thrombin is a potent angiogenic factor in the CAM system and in vivo. The activation of angiogenesis by thrombin is a receptor-mediated event (the receptor is referred to as protease-activated receptor, PAR-1) and is independent of fibrin formation (3,4).

Many cellular effects of thrombin on endothelial cells can contribute to the angiogenic action of thrombin:

1. Exposure of endothelial cells to thrombin cause a time and dose-dependent decrease in the attachment of these cells to basement membrane components (type IV collagen and laminin) with a concomitant increase in matrix metalloproteinase 2 activation (5).
2. Thrombin up-regulates the expression of integrin $a_v\beta_3$, the marker of the angiogenic phenotype of endothelial cells.
3. Thrombin has chemotactic and aptotactic effects on endothelial cells and binding of endothelial cells to thrombin suppress apoptosis.
4. Thrombin synergizes with the key angiogenic factor VEGF in endothelial cell proliferation by upregulation of the expression of VEGF receptors KDR & Flt-1 (6).

Furthermore, thrombin enhances the secretion of VEGF and matrix metalloproteinase 9 of PC3 human prostate cancer cells, leading to mutual stimulation of endothelial and cancer cells and increase the metastatic potential of cancer cells.

These results can explain the angiogenic and tumor promoting effect of thrombin and provide the basis for development of thrombin receptor mimetics or antagonists for therapeutic applications (7).

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